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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/624,362	07/23/2003	Pei Kan	38847-191328	7671

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EXAMINER	
SCHLIENTZ, NATHAN W	
ART UNIT	**PAPER NUMBER**
1616	

DATE MAILED: 08/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/624,362	KAN ET AL.	
	Examiner	Art Unit	
	Nathan W. Schlientz	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-38* is/are rejected.

7)☒ Claim(s) *4,6 and 24* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *7/23/03* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-38 are pending.

Claims 10 and 11 are the same as claims 28 and 29, respectively.

These claims are substantial duplicates and the applicant should cancel one of each duplicate or one of each duplicate will be cancelled upon allowance.

Claim Objections

1. Claims 4, 6 and 24 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. **Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.**

The limitation that the first phospholipid is selected from the group which consists of distearoyl phosphatidyl ethanolamine (DSPE) does not further limit the first phospholipid having a phase transition temperature between the range 40 and 70 °C. Also, the limitation that the second phospholipid is selected from the group which consists of dipalmitoleoyl phosphatidyl choline, dipalmitelaidoyl phosphatidyl ethanolamine, didecanoyl phosphatidyl choline, and dinonanoyl phosphatidyl choline does not further limit the second phospholipid having a phase transition temperature between the range -30 and 10 °C. According to the specifications, page 6 lines 11 through page 7 line 23, the phase transition temperatures of the said phospholipids are as follows: DSPE = 74 °C, dipalmitoleoyl phosphatidyl choline = -36 °C, dipalmitelaidoyl phosphatidyl ethanolamine = –33.5 °C, didecanoyl phosphatidyl choline = –34.7 °C, and

dinonanoyl phosphatidyl choline = –55.2 °C. These temperatures do not fall between the ranges set forth in claim 1.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 8-18, and 26-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The use of the limitation "derivative thereof" in claims 8-18, and 26-36, specifically "paclitaxel and/or a derivative thereof", "retinoic acid and/or a derivative thereof", and "camptothecin and/or a derivative thereof" throughout the pending claims render the claims indefinite, as it is not clear to which compounds is the applicant claiming. The various derivatives of compounds instantly claimed lead to a plethora of compounds, the scope of which is not clear. Accordingly, the metes and bounds of the claims are not clear.

4. Claim 21 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation in claim 21 "the liposome for incorporating high content of hydrophobic substances" on page 35, line 12 is indefinite. There is insufficient antecedent basis for the limitation "***the*** liposome" in the claim. The claim is directed

toward a specific liposome; however, in the instant case it is unclear to which liposome the applicant is referring.

5. Claim 37 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The use of the limitation "cholesterol derivative" in claim 37, line 21 renders the claim indefinite for similar reasons as discussed above for the use of "derivative thereof". The use of the term derivative leads to a number of possible compounds, and it is unclear to which derivative or derivatives of cholesterol the applicant intends to claim.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 8-18, and 26-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for liposomes comprising the hydrophobic substances paclitaxel, retinoic acid, and/or camptothecin, does not reasonably provide enablement for compositions comprising any derivatives of such hydrophobic substances. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Attention is directed to In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure

would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the nature of the invention
2) the state of the prior art
3) the relative skill of those in the art
4) the predictability of the art
5) the breadth of the claims
6) the amount of direction of guidance provided
7) the presence or absence of working examples
8) the quantity of experimentation necessary

The instant specification fails to provide guidance that would allow the skilled artisan to practice the instant invention without resorting to undue experimentation, as discussed in the subsections set forth herein below.

The claimed invention relates to a liposome formulation comprised of two varying phospholipids, differing based upon their structure and phase transition temperatures, encapsulating a hydrophobic drug such as paclitaxel, retinoic acid, or camptothecin. The recitation of "derivative thereof", with regards to the hydrophobic substances paclitaxel, retinoic acid, and camptothecin, throughout the pending claims encompasses a plethora of compounds, wherein determining the toxicity and efficacy of all such compounds for *in vivo* use requires undue experimentation. The specification does not provide guidance as to how one skilled in the art would go about selecting the polymer of choice in forming the instant compositions. Nor is guidance provided as to a specific protocol to be utilized in order to prove the efficacy of the presently claimed compositions in eliciting the desired response. Further, there are neither working examples nor teachings in the specification that enable one skilled in the art how to first identify the desired derivative, and second determine the desired drug/lipid ratio in order

to practice the claimed invention. Therefore, the claims and specifications fail to adequately provide enough guidance for one skilled in the art to practice the claimed invention without necessary undue experimentation.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1-3, 5-9, 18, and 19 are rejected to under 35 U.S.C. 102(b) as being anticipated by Sheih et al (Journal of Fermentation and Bioengineering, 1997).

The instant claims are directed toward a formulated liposome comprising: a first phospholipid, selected from a hydrogenated naturally-occurring phospholipid or a saturated phospholipid with long carbon chains (-$(CH_2)_n$-, the value of n is at least 14); a second phospholipid, selected from an unsaturated phospholipid or a saturated phospholipid with short carbon chains (-$(CH_2)_n$-, the value of n is at most 14); one or more hydrophobic substances; and liposome-forming materials.

Sheih et al disclose "a formulation for liposomes of egg phosphatidylcholine (EPC)/dimyristoylphosphatidylglycerol (DMPG) in 7:3 molar ratio together with 40% cholesterol, 25% α-tocopherol and 3% taxol (paclitaxel) (in mole/mole lipids) resulted in suitable sizes with good storage stability" (see page 88, Results and Discussion, 3rd paragraph). Therefore, Sheih et al anticipate the instant claims.

10. Claims 1-9, 18, and 19 are rejected to under 35 U.S.C. 102(b) as being anticipated by Straubinger et al US Patent 5,415,869.

Straubinger et al disclose a pharmaceutical formulation comprising: at least one taxane and one or more phospholipids (see claim 1). Straubinger et al further disclose the phospholipids being chosen from several phospholipids including: dipalmitoylphosphatidylserine and dioleoylphosphatidylcholine (see claim 2). Straubinger et al further disclose the pharmaceutical formulation with taxol (paclitaxel, see claim 6) and cholesterol and cholesterol derivatives (see claim 8). Therefore, Straubinger et al anticipate the instant claims.

11. Claims 1-7, 19, 21-25, and 37 are rejected to under 35 U.S.C. 102(b) as being anticipated by Scotto et al US Patent 4,873,089.

Scotto et al disclose a proteoliposome formulation comprising egg or soy phosphatidycholine (EPC or SPC) and hydrogenated egg or soy phosphatidylcholine (HEPC or HSPC) (see column 5, lines 37-64), as well as proteoliposomes comprising a saturated fatty acid, optionally cholesterol (see example 3, column 10, lines 24-45). Scotto also teaches the association of the said lipid vesicles with a drug (see column 8, lines 11-37). Therefore, Scotto et al anticipate the instant claims.

12. Claims 1-3, 5-9, 15, 16, 18, and 19 are rejected to under 35 U.S.C. 102(b) as being anticipated by Castor et al US Patent 5,776,486.

Castor et al disclose liposomes containing hydrophobic drugs. In particular, they disclose liposomes comprising phosphatidylcholine (PC), phosphatidylethanolamine

(PE), soy bean phosphatidylcholine (SPC), cholesterol, and paclitaxel or camptothecin. Therefore, Castor anticipates the instant claims.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

15. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 20 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scotto et al US Patent 4,873,089 in view of and Crosasso et al (Journal of Controlled Release (2000) 63, 19-30).

Scotto et al teaches liposome compositions comprising one type of phospholipids or a mixture of phospholipids including any unsaturated or saturated synthetic phosphatidylcholine (PC); egg of soy phosphatidylcholine (EPC or SPC) as a bulk phospholipid containing saturated phospholipids; dimyristoylphosphatidylcholine (DMPC); distearoylphosphatidylcholine (DSPC); dipalmitoylphosphatidylcholine (DPPC) and hydrogenated egg or soy phosphatidylcholine (HEPC or HSPC) (see column 4, lines 56-64). Scotto et al also teach the inclusion of a lipophilic molecule that can be included in the phospholipid bilayer including cholesterol and cholesterol derivatives (column 5, lines 14-33). Scotto et al further disclose the lipid vesicle associated with a drug or other biologically active or physiologically active agent (see column 8, lines 11-13), which includes hydrophobic substances.

The instant claims teach liposome formulations comprising a first and second phospholipid, one or more hydrophobic substances, and the liposome-forming material MPEG-DSPE. The difference between the instant claims and Scotto et al is that Scotto et al doesn't teach the addition of MPEG-DSPE with the liposome formulations. However, it is known in the art that polyethylene glycol conjugated, "PEGylated", liposomes have a longer circulation time in the bloodstream prior to being metabolized. Therefore, liposome formulations being used to carry drugs to target cells via intravenous injection benefit greatly from the addition of PEG or PEG derivatives by

allowing lower dose injections because the amount of drug reaching the target cells would be increased. It is for that reason the examiner joins Crosasso et al.

Crosasso et al teaches liposome preparations by employing hydrophilic polymer-conjugated phospholipid (methoxy polyethylene glycol-phosphatidylethanolamine) in order to enhance the liposomes circulation time in blood post iv administration. Crosasso et al further teaches the incorporation of cholesterol within the "PEGylated" (polyethylene glycol conjugated) liposomes comprising EPC, phosphatidylglycerol (PG), and paclitaxel. However, Crosasso et al does not teach liposomes comprising EPC or SPC and HEPC or HSPC.

Accordingly, in order to prolong the circulation in the bloodstream for the formulations of Scotto et al it would have been obvious to one skilled in the pertinent art at the time of the invention to combine those liposome compositions with MPEG-DSPE as in Crosasso et al. The persons skilled in the art would have had reason to expect the PEGylated liposomes comprising HEPC or HSPC and EPC or SPC, cholesterol, drug, and MPEG-DSPE would have delivered the said drug to the target cell more efficiently because of the prolonged circulation within the bloodstream.

17. Claims 1-19, and 21-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scotto et al US Patent 4,873,089 in view of Unger et al US Patent 5,733,572, and Castor et al US Patent 5,776,486.

Scotto et al teachings are discussed above. Scotto et al does not disclose the hydrophobic substances paclitaxel, retinoic acid, and camptothecin being encapsulated in their liposome formulations.

The difference between the claimed invention and the teachings of Scotto et al resides in the encapsulation of the specific hydrophobic substances paclitaxel, camptothecin, and retinoic acid. It is known in the art that liposome-based drug formulations are able to achieve the equivalent therapeutic efficacy to free drug, as well as reduce the systemic toxicity in many applications. Because of the toxicity associated with free paclitaxel, camptothecin, and retinoic acid it would be beneficial to incorporate these drugs within the liposome formulations of Scotto to reduce the toxic side effects. It is for that reason the examiner joins Unger et al and Castor et al.

Unger et al discloses dipalmitoylphosphatidylcholine (DPPC) liposomes incorporating vitamin A (retinoic acid) (see example 8, column 53, line 6-15). Unger et al, however, doesn't teach liposome formulations comprising a first and a second phospholipid, a liposome-forming material such as cholesterol, antioxidant, or PEGylated lipids.

Castor et al discloses encapsulation of paclitaxel or camptothecin within liposomes comprising EPC and cholesterol. However, Castor et al doesn't disclose the use of a first and second phospholipid chosen based upon their phase transition temperatures.

Accordingly, it would be obvious to one skilled in the pertinent art at the time of the invention to employ the liposomes of Scotto et al in combination with any hydrophobic substance of Castor et al and/or Unger et al, because the persons skilled in the art would have had a reasonable expectation of success in conventionally encapsulating a drug of choice (paclitaxel, retinoic acid, or camptothecin) within the

liposomes of Scotto et al and reducing the side effects associated with the toxicity of the drugs.

Conclusion

No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nathan W. Schlientz whose telephone number is 571-272-9924. The examiner can normally be reached on 8:00 AM to 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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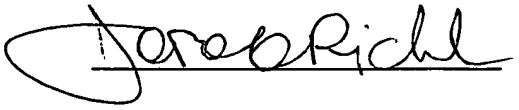

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